LYME DISEASE: Guidelines for Wisconsin Health Care Providers

I. BACKGROUND

Lyme disease is a multisystem disorder caused by the spirochete *Borrelia burgdorferi*. The causative agent is transmitted by the bite of certain ticks in the genus *Ixodes*. The most common clinical manifestation is a skin lesion, erythema migrans (EM), followed in some patients by rheumato-logic, neurologic, and cardiac abnormalities.

Portions of the syndrome now called Lyme disease were initially described in Europe as early as 1909. The first reported case in the USA occurred in Wisconsin in 1969. The disease was first fully described after Steere and colleagues investigated an unusual cluster of illnesses resembling juvenile rheumatoid arthritis which occurred near Lyme, Connecticut in 1975. Subsequent investigations identified *B. burgdorferi* as the etiologic agent of Lyme disease and identified the tick *Ixodes scapularis* (formerly called *Ixodes dammini*) as the principal vector of the spirochete in the USA.

A. Etiology

Borrelia burgdorferi is a motile, slow growing spirochete with a generation time *in vitro* of 12-24 hours. The organism is readily killed by drying and by exposure to disinfectants. *Borrelia burgdorferi* can persist in some untreated patients for years.[1] The mechanism by which small numbers of *B. burgdorferi* produce protean disease in their host, despite an active humoral and cellular immune response, is still unclear.

B. Transmission

Lyme disease is acquired from the bite of an infected tick. *Ixodes scapularis*, commonly called the deer tick, is the only known vector of *B. burgdorferi* in Wisconsin. The current geographic range of *I. scapularis* in Wisconsin is shown in Figure 1. Although *B. burgdorferi* has been detected in other blood-feeding arthropods such as the American dog tick (*Dermacentor variabilis*, sometimes commonly but erroneously called the wood tick), mosquitoes, fleas, and tabanid flies (deer flies, horse flies), the presence of the spirochete in these arthropods is ephemeral, and there is no convincing laboratory or epidemiologic evidence that they have any role in transmission of the pathogen.[2,3,4]

There is no evidence to support person-to-person transmission. Transplacental transmission has been reported, but epidemiologic studies suggest that adverse birth outcomes are rare.[5,6] Transmission of *B. burgdorferi* by the transfusion of blood obtained from a spirochetemic donor has never been reported, despite the theoretical possibility of this mechanism.[7]

II. EPIDEMIOLOGY

A. Wisconsin Surveillance

The Wisconsin Division of Public Health (DPH) has conducted surveillance for Lyme disease since 1980; the disease is officially reportable in Wisconsin. The surveillance system is based on passive reporting of cases by clinics and physicians. All patients with Lyme disease are to be reported to the local public health department in the jurisdiction where the patient resides; the reports are then forwarded to the Wisconsin DPH. The Wisconsin surveillance case definition is the same as the national case definition: *a person with physician-diagnosed EM (solitary lesion must be ≥ 5 cm diameter), or who has at least one late manifestation of the disease (rheumatologic, neurologic, cardiac) and laboratory confirmation of infection.* It should be noted that this is an epidemiologic case definition intended for purposes of surveillance only. The Wisconsin Lyme disease case report form, with a more detailed case definition, is included as an attachment to this publication.

B. Epidemiology in Wisconsin

A cumulative total of 6,089 cases of Lyme disease (which met the then-operant case definitions) have been reported to the DPH from 1980 through 1998. Although reported cases are geographically widespread, the majority of case-patients whose geographic site of likely exposure could be ascertained acquired the infection in the northwestern and westcentral parts of Wisconsin. Predictably, these areas also have the highest reported incidence of Lyme disease (Figure 2). The disease is highly seasonal; over 80% of Wisconsin cases with EM lesions had onset during May through August. This corresponds with the feeding activity of the nymphal stage of *I. scapularis*.

Figure 1. Known geographic range of I. scapularis *by county, Wisconsin, 1997.*

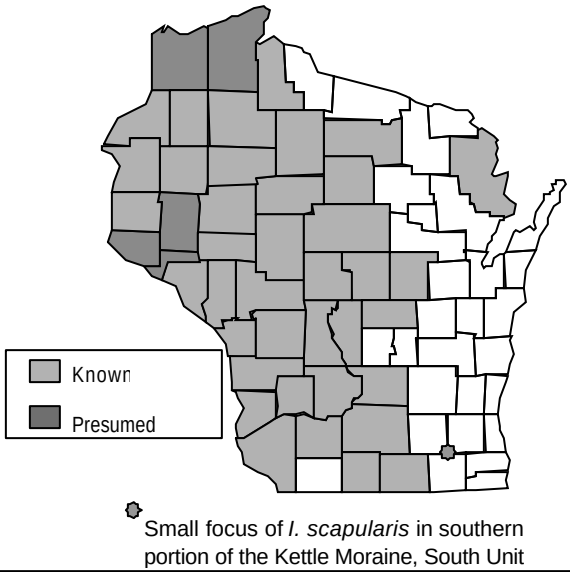
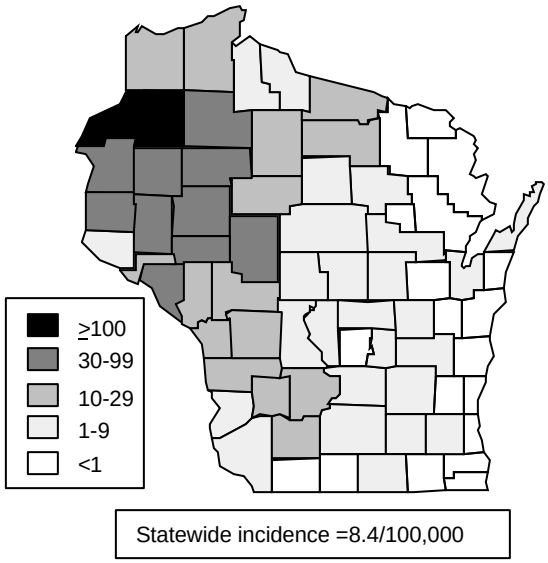


Figure 2. Mean annual Lyme disease incidence per 100,000 persons by county of residence, Wisconsin, 1993-1997



C. <u>Epidemiology in the United States</u>

Lyme disease is the most commonly reported vector-borne illness in the USA. From 1982 through 1997, 111,943 cases were reported to the Centers for Disease Control and Prevention (CDC). Although cases have been reported in residents of 49 states, 89% of all cases have been reported from the 10 states with the highest reported incidence of Lyme disease. These are (in decreasing order of incidence for 1997): Connecticut, Rhode Island, New Jersey, New York, Pennsylvania, Delaware, Maryland, Wisconsin, Minnesota, and Massachusetts.

III. CLINICAL MANIFESTATIONS

The clinical spectrum of Lyme disease is commonly categorized as early localized, early disseminated, and late disseminated disease. These stages can overlap but may also occur independently; an untreated patient may experience one or several of these manifestations over time. Notably, fewer than half the patients with Lyme disease recall an antecedent tick bite.

Usually, the first sign of early localized disease is erythema migrans (EM), appearing from 3 to 32 days (mean 9 days) after a tick bite. EM is the most distinctive clinical marker of Lyme disease; however, in about 25% of patients the lesion either goes unnoticed or does not occur. This lesion typically begins at the site of the tick bite as a red macule or papule with an erythematous annular border, and expands over days to weeks, often (but not always) exhibiting partial central clearing as it enlarges. Although the EM lesion is typically flat, smooth, and asymptomatic, it can less frequently be pruritic, indurated, centrally vesicular, or purpuric-hemorrhagic. The expansion of the EM lesion and the lack of pruritis help to differentiate it from a hypersensitivity reaction to an insect bite. EM is self-limiting, and generally will fade within four weeks without treatment.[8] Patients with early localized disease will frequently experience regional lymphadenopathy and modest constitutional symptoms such as headache, low grade fever, and myalgias.

Days to weeks following initial infection, *B. burgdorferi* can disseminate from the site of inoculation and produce manifestations of early disseminated Lyme disease. In this stage, multiple secondary EM lesions may occur. These secondary lesions lack the central papule seen in primary EM lesions. They may be few or many in number, can be widely distributed and may show confluence. Constitutional symptoms and generalized lymphadenopathy are common. Within weeks to months, some patients experience rheumatologic, neurologic, or cardiac involvement. Untreated patients may develop late stage disseminated disease months to years after initial onset. The commonly occurring manifestations of Lyme disease in the USA are listed in Table 1. Of

note, Lyme disease-related arthritis is typically intermittent, migratory, and oligoarticular, most commonly affecting the large joints, especially the knee. Symmetric unremitting polyarthritis is unlikely to be due to Lyme disease.

Table 1. Signs and symptoms commonly associated with Lyme disease in the USA [8,9,10,11]

STAGE OF DISEASE	SIGNS AND SYMPTOMS	PATIENTS WITH FINDINGS (%) [a]
Early Localized Disease	Erythema migrans (localized lesion)	60-80
	Constitutional symptoms (minor)	n/a [b]
	Low grade fever	n/a
	Regional lymphadenopathy	41
Early Disseminated Disease	Multiple EM lesions	17-50
	Constitutional symptoms:	
	- malaise, fatigue, lethargy	80
	- headache	64
	- fever, chills	59
	- stiff neck	48
	- arthralgias	48
	- myalgias	43
	Generalized lymphadenopathy	20
• ***Rheumatologic***		
	Arthritis (typically intermittent and oligoarticular, especially knees and other large joints)	51-60
• ***Neurologic***		
	Meningitis [c]	15-20
	Cranial neuritis (especially facial palsy)	n/a
	Radiculoneuropathy	n/a
	Subtle encephalopathy	n/a
• ***Cardiac***		
	Atrioventricular block	4-8
Late Disseminated Disease	Chronic arthritis	11
	Myopericarditis	n/a
	Neurologic impairment (especially subacute encephalopathy)	n/a
	Fatigue	n/a

[a] Percentages refer to the proportion of all patients diagnosed with Lyme disease. Treatment in the early stages of the disease will reduce the proportion of patients who manifest late disease. Percentages are study-specific and are not population based.
[b] n/a = not available
[c] Lyme disease-associated meningitis typically has a lymphocytic pleocytosis, often presenting as an "aseptic" meningitis.

Various other signs and symptoms have been described in persons diagnosed with Lyme disease; however, they are not typical of the disease acquired in the USA and for some of these syndromes, it is not known if there is a causal association with *B. burgdorferi* infection. For early disseminated Lyme disease these include: lymphocytoma, myositis, chorea, cerebellar ataxia, conjunctivitis and other ophthalmic abnormalities, hematuria, proteinuria, and orchitis. For late Lyme disease these include: acrodermatitis chronica atrophicans, chronic encephalomyelitis, ataxic gait, chronic axonal polyradiculopathy, Tourette's syndrome, dementia, verbal memory impairment, depression, keratitis, panophthalmitis, and other ophthalmic abnormalities.[8,12,13,14,15,16] Lymphocytoma and acrodermatitis chronica atrophicans have been frequently described in Europe, probably due to different strains of *B. burgdorferi* circulating on that continent.

IV. LABORATORY DIAGNOSIS

In general, laboratory testing remains an adjunct tool in the diagnosis of Lyme disease. Unless *B. burgdorferi* is actually isolated from a clinical specimen, the diagnosis of Lyme disease should be viewed as a probability assessment made after consideration of the patient's clinical presentation, exposure risk, and laboratory findings.

A. Antigen Detection

With current techniques, attempts to detect *B. burgdorferi* in clinical specimens are of limited utility to the clinician. Cultivation of the organism from a skin biopsy specimen obtained at the margin of an EM lesion has the highest probability of success, but patients who present with classic EM seldom pose a diagnostic challenge that would necessitate such measures. Attempts to culture *B. burgdorferi* from blood, cerebrospinal fluid, or synovial fluid are considerably less successful. A specialized medium for culturing *B. burgdorferi* is available through some reference laboratories.

The polymerase chain reaction assay (PCR) is capable of detecting *B. burgdorferi* nucleic acid in clinical specimens. It must be recognized that the PCR assay cannot differentiate viable spirochetes from spirochetal nucleic acid fragments which may persist in specimens from adequately treated patients. Because of the extreme sensitivity of the assay and the potential for false positive results, PCR testing should only be performed by an experienced research facility and should be used selectively, when other diagnostic tests have not been useful.

B. Serologic Diagnosis

Although serologic assays can be a valuable aid in the diagnosis of Lyme disease, these tests *per se* cannot definitively diagnose the disease. Because of the limitations of serologic testing for *B. burgdorferi*, the CDC and the Association of State and Territorial Laboratory Directors recommend that sera be tested using a sensitive initial test (enzyme immunoassay [EIA] or immuno-fluorescent assay [IFA]), and that all specimens initially found to be positive or equivocal be tested using the more specific Western blot assay (WB).[17]

1. Testing recommendations - Early localized and early disseminated Lyme disease (Figure 3)

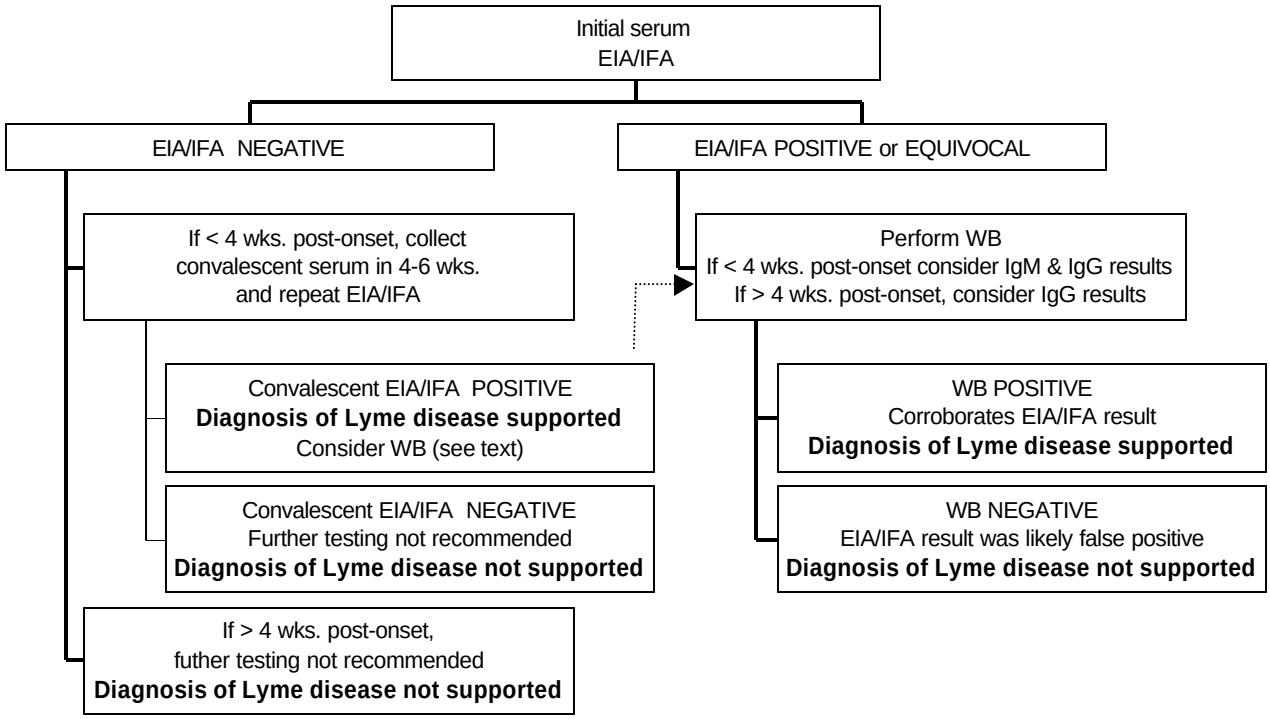
Serologic testing lacks sensitivity in early Lyme disease. Typically, the initial antibody response (IgM response) will not become detectable until three to four weeks after exposure. Of patients with EM, only 40-50% will have diagnostically significant antibody titers.[18] Clinicians seeking serologic support for a diagnosis of early Lyme disease should submit serum for testing by an IgM-specific EIA or IFA. Patients with disease of longer duration (more than four to six weeks) can be tested using a polyvalent EIA/IFA. Serologic studies are generally unnecessary for patients who have classic EM and a compatible exposure history. The initiation of antibiotic therapy during early Lyme disease can abrogate the antibody response in a minority of patients.

If the initial EIA/IFA is positive or equivocal, a WB should be requested. The duration of the illness dictates WB interpretation. For a specimen collected during the first four weeks after symptom onset, both IgM and IgG WB results should be considered. A positive IgM WB result on a serum collected within four weeks of onset is supportive of a diagnosis of Lyme disease (the IgG WB may be negative for patients with Lyme disease who have been only recently exposed). For patients with symptom duration of over four weeks, a positive IgG WB result supports a diagnosis of Lyme disease; the IgM response for such patients is variable and should not be relied upon.[17] A negative WB suggests that the prior EIA result was falsely positive, and that alternate diagnoses should be considered.

Serum which tests negative on the initial EIA/IFA need not be tested further unless there is a possibility that the specimen was obtained before the patient seroconverted. In that case, a convalescent sample, collected four to six weeks after the first, should be submitted for testing by EIA/IFA. If this convalescent sample is negative, it is unlikely the patient has Lyme disease, and no further testing is recommended. If the convalescent sample is positive (i.e., sero-conversion is documented), the patient probably has been acutely infected with *B. burgdorferi*. Whether a WB should be performed on the positive convalescent serum to confirm the specificity of the EIA/IFA test depends upon the strength of the clinical and epidemiologic evidence of Lyme disease, and the magnitude of the titer change between the paired sera. It may not be necessary nor cost effective to perform a WB for the patient who has a very suggestive illness, a compatible exposure history, and a significant rise in titer between the acute and convalescent serologic test results. In the absence of such evidence, or if there is a possibility of another recently acquired disease which could account for the seroconversion (e.g.

syphilis, leptospirosis, infectious mononucleosis – see Section 4 below), a WB should be considered.

Figure 3. Testing algorithm for suspected Lyme disease.



2. Testing recommendations - Late persistent Lyme disease (Figure 3)

Untreated patients with manifestations of late disseminated Lyme disease nearly always have diagnostically significant levels of IgG antibody in their sera. Thus, the sensitivity of a single EIA/IFA is high for these patients. Because of the potential for false positives due to cross-reactive antibody (discussed in Section 4 below), an IgG WB should be performed on serum which tests positive or equivocal on the EIA/IFA. A negative WB result on such a specimen suggests that the initial EIA/IFA result was falsely positive, and alternate diagnoses should be considered.

In patients with suspected neuroborreliosis, the detection of antibody to *B. burgdorferi* in the cerebrospinal fluid (CSF) can have diagnostic significance, particularly if the concentration of specific antibody in the CSF is greater than that in the serum, indicating intrathecal antibody production.

3. Western Blot interpretation [17]

An IgM immunoblot should be considered positive if at least two of the following three bands are present: 24 kDa (OspC), 39 kDa, and 41 kDa.

An IgG immunoblot is considered positive if at least five of the following ten bands are present: 18 kDa, 21 kDa (OspC), 28 kDa, 30 kDa, 39 kDa, 41 kDa, 45 kDa, 58 kDa, 66 kDa, and 93 kDa. The apparent molecular mass of outer surface protein C (OspC) is strain dependent; thus the 21 kDa and 24 kDa proteins referred to above are the same.

4. Other serologic testing considerations

Detectable IgG antibody may persist for years, even in patients that received successful antibiotic therapy. This antibody longevity, coupled with the fact that

about 8-11% of clinically normal persons in endemic areas are EIA/IFA positive[19,20] means that a diagnostically significant level of antibody does not necessarily indicate a causal relationship between *B. burgdorferi* infection and a patient's current clinical illness. Although treated patients usually have slowly decreasing antibody titers, the persistence of antibody precludes the use of follow-up titers to assess treatment efficacy. The relatively high rate of seropositivity among clinically normal individuals living in endemic areas and the poor positive predictive value of these tests performed on such persons means that the use of serology to "screen" normal populations for Lyme disease is an inappropriate use of the test.

False positive EIA/IFA results can occur in patients infected with other spirochetes (other *Borrelia* sp., *Treponema* sp., Leptospires) because antibodies to these related organisms may cross react on *B. burgdorferi* serology. Patients with syphilis will have positive VDRL and RPR tests, whereas Lyme disease patients will not. Additionally, false positive reactions have been reported in patients with rheumatoid arthritis, systemic lupus erythematosus, and infectious mononucleosis.

V. TREATMENT (Table 2)

A. Erythema migrans and early febrile illness

Effective drugs during this stage include oral doxycycline, amoxicillin, and cefuroxime axetil. Most patients treated appropriately during the early stage of Lyme disease do very well, with infrequent objective evidence of treatment failure, although a minority of patients may continue to have residual symptoms such as fatigue, headache, and arthralgias. These sequellae persist for varying lengths of time and are rarely, if ever, responsive to additional antibiotic therapy.[21]

B. Neurologic manifestations

Intravenous regimens are recommended for virtually all neurologic manifestations of Lyme disease with the exception of isolated facial nerve palsy (Table 2). Treatment of patients with isolated facial nerve palsy may not affect the resolution of the palsy nor the median time it takes to resolve; the great majority of these patients recover completely with or without antibiotic intervention.[21] The principal reason to treat these patients is to prevent the development of signs of later persistent Lyme disease. Some experts recommend a lumbar puncture for patients with Lyme disease-related facial palsy, and subsequent parenteral antibiotics if a pleocytosis is present. Others advise that these patients be treated with oral regimens if symptoms of meningitis or radiculoneuritis are not present. Persistent facial paresis which persists after appropriate therapy typically indicates unresolved damage to the facial nerve, and does not necessarily indicate continuing infection.

C. Cardiac manifestations

Patients with early Lyme disease who have first-degree atrioventricular block (PR interval < 0.3 seconds) and no history suggesting higher degree block, may be treated with oral doxycycline or amoxicillin for 21-28 days. Although comparative studies have not been performed, intravenous ceftriaxone is recommended for patients who have second- or third-degree atrioventricular block, or who have other serious cardiac abnormalities. Patients with serious conduction disturbances may require temporary transvenous pacing. Corticosteroid therapy may be considered for patients with severe carditis who do not respond to antibiotics within 24 hours.[22]

D. Rheumatologic manifestations

Lyme arthritis has been treated successfully with both oral and parenteral antibiotics. Thus, an oral regimen similar to that used for early Lyme disease but given for a longer duration is recommended as the initial treatment.[27] Parenteral antibiotics should be considered for those patients who do not respond to an appropriate oral regimen. The use of corticosteroids has been associated with nonresponsiveness to antibiotic therapy and should be avoided, at least until two courses of appropriate antimicrobial therapy are completed. Some experts also advise that a negative PCR assay on the synovial fluid be obtained before corticosteroids be considered.[27] Some patients with Lyme arthritis of the knee which persisted after adequate antibiotic treatment have been treated successfully with synovectomy.[21,27] There is evidence that Lyme disease may trigger fibromyalgia syndrome in some patients; this sequella does not respond to further antibiotic therapy.[21,22]

E. Treatment during pregnancy

Information currently in the medical literature is inconclusive regarding the frequency or precise risk to the fetus of transplacental transmission of *B. burgdorferi*. However, the risk of adverse pregnancy outcomes appears to be low and is likely associated with an acute onset of untreated maternal Lyme

disease during early pregnancy.[5,6,28] The optimum therapy during pregnancy is likewise unclear. It may be sufficient to treat Lyme disease during pregnancy using the same regimens appropriate for non-pregnant patients with similar clinical manifestations,[26] although doxycycline or other tetracycline congeners should not be used in pregnant or lactating women. Other authorities advise intravenous regimens for all cases of Lyme disease in pregnant women except for those who present with an isolated EM lesion and no associated signs or symptoms of disseminated disease.[21]

F. <u>Asymptomatic seropositive patients</u>

There is no evidence to suggest that seropositive patients who are asymptomatic should be treated with antibiotics, nor should asymptomatic persons be "screened" for antibodies to *B. burgdorferi*.

G. <u>Post-tick bite treatment considerations</u>

It is clear that the risk of contracting Lyme disease from a deer tick bite, even in endemic areas, is low, averaging only 1.4% among untreated patients enrolled in several prospective studies on post-tick bite antibiotic prophylaxis.[29] These placebo-controlled studies do not support the routine use of antibiotics after a recognized tick bite. Animal studies have shown that the transmission of *B. burgdorferi* from *I. scapularis* ticks does not occur within the first 24 hours of tick attachment, and is minimal during the next 24 hours. Thus, knowing that a tick had been removed soon after attachment should alleviate fears of transmission and obviate the need to consider antibiotic prophylaxis. The testing of removed ticks for the presence of *B. burgdorferi* is not routinely recommended because the sensitivity of such testing is unknown and may potentially produce falsely negative results.

Table 2. Recommendations for antimicrobial therapy of Lyme disease.[8,21,22,23,24,25,26,27]

MANIFESTATION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE [a]
I. EM and early febrile illness			
• *First line* [b]	Doxycycline [c]	100 mg p.o. bid x 14-28 days	(≥9 yrs) 100 mg p.o. bid x 14-28 days
	Amoxicillin	500 mg p.o. tid or qid x 14-28 days	20-50 mg/kg/day p.o. divided tid x 14-28 days
• *Alternative*	Cefuroxime axetil	500 mg p.o. bid x 14-28 days	250 mg p.o. bid x 14-28 days
• *Second line*	Erythromycin [d]	250-500 mg p.o. tid x 21 days	30 mg/kg/day p.o. divided tid x 21 days
II. Neurologic			
A. facial palsy alone	Same oral regimens as for EM and early febrile illness; treat for 21-28 days.		
B. more serious or generalized disease			
• *First line*	Ceftriaxone	2 g IV q d x 14-28 days [e]	75-100 mg/kg/day IV x 14-28 days (Not to exceed 2 g / day)
• *Second line*	Penicillin G	20 million units/day IV divided q 4h x 14-28 days [e]	300,000 units/kg/day IV divided q 4h x 14-28 days
III. Cardiac			
A. mild (PR interval <0.3 sec)	Same oral regimens as for EM and early febrile illness; treat for 21-28 days.		
B. more severe			
• *First line*	Ceftriaxone	2 g IV q d x 14-28 days [e]	75-100 mg/kg/day IV x 14-28 days (Not to exceed 2 g / day)
• *Alternative*	Penicillin G	20 million units/day IV divided q 4h x 14-28 days [e]	300,000 units/kg/day IV divided q 4h x 14-28 days
IV. Rheumatologic	Same oral regimens as for EM and early febrile illness; treat for 30-60 days		
- If no response to oral antibiotics:			
• *First line*	Ceftriaxone	2 g IV q d x 14-28 days	75-100 mg/kg/day IV x 14-28 days (Not to exceed 2 g / day)
• *Alternative*	Penicillin G	20 million units/day IV divided q 4h x 14-28 days	300,000 units/kg/day IV divided q 4h x 14-28 days

[a] Pediatric dose should not exceed adult dose.
[b] Because of its activity against *Ehrlichia*, doxycycline may be preferred for post-tick bite patients who are febrile and do not have EM, or if clinical and/or laboratory findings are suggestive of ehrlichiosis.
[c] Use of doxycycline to treat Lyme disease should be avoided during pregnancy or lactation, or in children under 9 years old.
[d] Erythromycin is not as effective as the other oral agents cited in this table.
[e] Treatment duration is typically 14 days. For persistent symptoms, continue for an additional 14 days.

H. Considerations for "treatment failures"

In patients with long-standing Lyme disease, the clinical response to antibiotic therapy can be slow, sometimes taking up to six months post-treatment.[26] However, if signs and symptoms do persist after a reasonable period of time has elapsed, the clinician should consider the following points.

1. Reevaluation of the original diagnosis

Consider that the initial diagnosis of Lyme disease may have been in error. Thus, the possibility of other etiologies or conditions needs to be explored. A careful history and physical examination should be repeated, serologic testing for Lyme disease should be repeated in a reference laboratory, and equivocal or positive results should be confirmed by Western blot assay.

2. Reevaluation of the patient's initial treatment regimen

The cause of persistent illness may be due to inadequate or improper prior therapy. In such a circumstance, retreatment with an appropriate antimicrobial regimen should be considered (Table 2).

3. Ongoing infection or recurrent illness after appropriate therapy

Persistent illness among previously treated, serologically confirmed (WB positive) patients which cannot be explained by other diagnoses may result from persistent *B. burgdorferi* infection. A WB assay which shows new bands (i.e., an expansion of the antibody response) when compared with the patient's original WB performed prior to treatment is suggestive of ongoing infection. In such cases, the clinician may consider:

- A full course of a recommended alternative regimen (Table 2).
- The use of a parenteral regimen if the initial regimen had been oral.
- Adjunct therapy with anti-inflammatory agents for patients who did not respond to a repeated course of antibiotics (the early use of corticosteroids has been associated with nonresponsiveness to antibiotic therapy).
- Retreatment with the same antibiotic regimen employed initially, with the proviso that the initial treatment was appropriate. However, repeated courses of parenteral therapy are generally not advised except in refractory CNS disease confirmed by diagnostic testing.
- The use of arthroscopic synovectomy for patients with chronic synovitis which is nonresponsive to a repeated course of antibiotic therapy.

Apparent responses to repeated courses of antibiotics, sometimes with subjective recurrence of symptoms soon after the completion of therapy, can have several possible explanations. These include nonspecific anti-inflammatory effects of certain antimicrobials, the existence of other unknown or misdiagnosed conditions which responded to the therapy, placebo effect, and, rarely, true persistent Lyme disease. In all cases, the patient should be periodically re-assessed. The development of new or progressive signs or symptoms should not automatically be ascribed to Lyme disease.

4. Reinfection

Reinfection with *B. burgdorferi* has been described in patients who had been treated early during their first episode of Lyme disease, but occurs only rarely in patients with longer-standing disease who presumably had an expanded immune response to the initial infection. Although this suggests some degree of naturally-acquired immunity, its durability is unclear, and patients should be cautioned that reinfection is possible. If reinfection does occur, standard treatment recommendations for the current stage of Lyme disease are indicated.

5. Sequellae of B. burgdorferi *infection*

Patients with recurrent or persistent symptoms after adequate antibiotic therapy may have syndromes triggered by the initial infection, but which are not due to the persistence of viable *B. burgdorferi*. These patients would not be responsive to additional courses of antimicrobials. Examples of such syndromes include fibromyalgia;
permanent tissue damage resulting from the original infection; poorly degraded, dead *B. burgdorferi* organisms causing a focus of sterile inflammation; and immunologic or autoreactive sequellae such as reactive arthritis or autoimmune neuropathy.[26]

6. Coinfection with other tick-borne pathogens

In Wisconsin, *I. scapularis* ticks can also transmit the agents of babesiosis and human granulocytic ehrlichiosis. These diseases share certain clinical signs and symptoms with Lyme disease. Co-infection with these agents and *B. burgdorferi* has been described in humans as well as in the vector tick, and more than one of these pathogens may possibly be

transmitted by the same tick bite. Specific tests exist for babesiosis and ehrlichiosis. Brief discussions of these two diseases can be found in Section VII.

VI. PREVENTION

A. Tick avoidance

Within their geographic range (Figure 1), deer ticks are found primarily in wooded, brushy areas that provide cover and forage for their mammalian hosts as well as the shade and high humidity the tick needs to survive. Ticks "quest" (seek a host) by climbing to the tips of grass blades or shrubs. When the host brushes up against a questing tick, the tick sticks to the host's skin or clothing. The tick usually will crawl upwards until it finds bare skin on which to attach and begin feeding. It will anchor its mouthparts into the skin of the host and remain tenaciously attached at that site, feeding on blood for several days. The tick "bite" is painless.

B. Removal of attached ticks

It is important that attached ticks be removed promptly (see "post-tick bite treatment considerations" above). The tick should be grasped with thin-bladed forceps as close to its mouthparts as possible, and a gentle traction should be applied for 15-30 seconds to loosen the tick's attachment and allow the tick to be removed. Do not apply pressure to the body of the tick, since this may cause any bacteria present within the tick gut to be expressed into the patient. Similarly, avoid the use of "folk remedies" for tick removal such as the application of Vaseline, petroleum solvents, or a hot match to the tick. Such remedies are ineffective, and the noxious stimulus may result in the regurgitation of pathogens into the tick's host.

C. Personal preventive measures

Because prompt removal of ticks is important, the thorough checking of one's body for ticks after being in tick habitat is a key prevention element. Such inspections should be performed at least daily, and parents should be encouraged to check their young children. Due to the small size of deer ticks they may sometimes be more easily felt with the fingertips than visually detected, especially if they are in the scalp.

Environmental modifications, such as clearing brush, mowing tall grass, and widening trails can help reduce the chances of encountering ticks. When possible, avoidance of tick habitat is advisable, e.g., walking in the center of cleared trails or refraining from sitting on the ground. Protective dress is also helpful when in tick endemic areas. Long pants tucked into socks or boots, closed shoes (not sandals), and long sleeved shirts tucked into pants can help keep ticks on one's clothing rather than on skin. Light-colored clothing will make ticks easier to detect.

Effective tick repellents include DEET (n,n-diethyl-m-toluamide) and permethrin. DEET is widely available in multiple commercial products and is approved for use on skin as well as clothing. Although uncommon, reports of both local allergic reactions and systemic toxicity have been associated with the use of DEET. It also needs to be re-applied after several hours. Considering that repellents with 20-30% DEET concentrations are about 90% effective in repelling deer ticks,[30] the slight increase in efficacy that might be realized with the use of higher concentrations of DEET should be weighed against the increased cutaneous absorption of the chemical. Absorption of DEET can also be minimized by applying only to exposed skin and by washing repellent-treated skin after coming indoors. Permethrin both kills and repels ticks. Commercial products containing 0.5% permethrin (e.g., Permanone™, Duranon™) are approved for use on clothing as a tick repellent. Their efficacy on clothing can last for days following a single application. Repellents containing permethrin are not approved for use on skin.

D. Vaccination

In December of 1998, the Food and Drug Administration approved a license application for the first vaccine designed to prevent Lyme disease in humans. That vaccine, called LYMErix™, contains recombinant outer surface protein A (OspA) of *B. burgdorferi*. At the time of this writing (February, 1999), FDA approval is pending on yet another OspA vaccine. These OspA vaccines work by neutralizing or killing *B. burgdorferi* in the gut of the deer tick before the spirochete can be transmitted to the tick's host. An efficacy of 50% and 79% has been shown after the second and third doses of LYMErix™, respectively, in a large (>10,000 subjects), placebo-controlled, double blind trial. Although the optimum vaccination schedule is still under review, the currently approved schedule is for three doses of the vaccine to be given at 0, 1, and 12 months. The vaccine is not approved for children under 15 years of age. Duration of immunity, and thus the need for periodic boosters, is not yet known. The Advisory Committee on Immunization

Practices (ACIP) of the CDC is developing recommendations on the use of this vaccine.

Vaccination against Lyme disease may become an important component of efforts to reduce disease incidence, but the vaccine is not recommended for everyone. Rational use of the vaccine by clinicians will require an estimate of the individual patient's risk of contracting Lyme disease. This risk is based on the endemicity of the geographic areas in which the patient lives, works, and recreates, as well as the patient's lifestyle - i.e., the amount of time spent outdoors in tick habitat during late spring through early autumn. Vaccinated patients should be cautioned not to ignore measures to avoid tick bites, since they will remain susceptible to other endemic tick-borne diseases such as ehrlichiosis and babesiosis, and because the vaccine is not 100% efficacious in preventing Lyme disease.

Because the vaccine will produce a detectable antibody titer to *B. burgdorferi*, it has the potential to complicate the interpretation of current serologic tests like the EIA. However, vaccine-induced antibody can be distinguished from infection-induced antibody by the WB assay, making this technique even more critical when testing vaccinated individuals.

VII. OTHER TICK-BORNE DISEASES IN WISCONSIN

A. Human granulocytic ehrlichiosis (HGE)

The rickettsia-like agent of HGE is transmitted by *I. scapularis* which is also the vector of *B. burgdorferi*. During 1997, 45 cases of HGE were identified in northwestern Wisconsin through a special active surveillance project. Ehrlichiosis will soon become a notifiable condition in the state of Wisconsin, and in the interim, voluntary reporting of ehrlichiosis is strongly encouraged. Coinfection of the HGE agent and *B. burgdorferi* have been described in humans as well as in the vector tick.

Although only HGE is endemic in Wisconsin, imported cases of human monocytic ehrlichiosis (HME) have been diagnosed here. Clinically, HGE and HME are indistinguishable. After an incubation period of approximately 7-21 days, common signs and symptoms of HGE include fever, malaise, severe headache, shaking chills, and diaphoresis. Less commonly observed are lymphadenopathy, abdominal pain, nausea, vomiting, diarrhea, cough, arthralgia, skin rash (usually maculopapular), anorexia, and changes in mental status. Common laboratory findings include thrombocytopenia, leukopenia, anemia, and modestly elevated liver transaminase levels.[31] Specific diagnosis of HGE can be made by the direct visualization of aggregates of ehrlichiae in the cytoplasm of neutrophils on a Wright-stained blood smear, by demonstrating a significant rise in specific antibody to the HGE agent, or by PCR assay. Performing a combination of these tests may improve diagnostic sensitivity. Tests designed to diagnose HME may not detect HGE infection.

Most cases respond rapidly to doxycycline therapy (3mg/kg per day divided bid). The optimum duration of therapy is not yet known. There are no clinical data on alternatives to doxycycline for the treatment of HGE in children under the age of 9 years or of pregnant women (groups for whom tetracycline congeners are routinely contraindicated). In general, even if the diagnosis of ehrlichiosis is unproven, clinicians should consider doxycycline treatment for patients who have an unexplained febrile illness after tick exposure, especially if the patient is thrombocytopenic or leukopenic.

B. Babesiosis

Babesiosis is a malaria-like illness caused by *Babesia microti*, a protozoan which parasitizes erythrocytes. In the upper midwest, the etiologic agent is transmitted by *I. scapularis* ticks, and cases of concurrent infections with *B. microti*, *B. burgdorferi,* and the HGE agent have been described.[32] Occasionally, cases of babesiosis have been acquired by blood transfusions from asymptomatic but parasitemic donors. Although not officially reportable in Wisconsin, a small number of cases are known to have been acquired in the northwestern and westcentral parts of the state.[33,34]

The clinical spectrum of babesiosis ranges from a mild, self-limited illness to a fatal disease. More severe cases tend to occur in patients who are asplenic, elderly, or who are otherwise immunosuppressed. Babesiosis can cause fever, chills, fatigue, myalgias, arthralgias, and jaundice secondary to hemolytic anemia. Supportive laboratory findings include thrombocytopenia, anemia, and hepatic dysfunction. The illness is most frequently diagnosed by the identification of the protozoan within erythrocytes on a blood smear. Serologic and PCR assays, as well as animal inoculation, can also be used to diagnose babesiosis. Treatment is with clindamycin and quinine; exchange

transfusion may be necessary for patients who are heavily parasitized.

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ACKNOWLEDGEMENTS AND CREDITS

This document was prepared by Dr. James Kazmierczak, Epidemiologist, Bureau of Communicable Diseases, Wisconsin Division of Public Health; and was reviewed by Dr. Jeffrey Davis, Chief Medical Officer and State Epidemiologist for Communicable Diseases, Wisconsin Division of Public Health.

We wish to sincerely thank the panel of experts who reviewed this document for their valuable comments and suggestions. This panel included: Drs. William Agger, Michael Finkel, Fergus McKiernan, Paul Mitchell, and the staff of the CDC's Lyme Disease Program within the Bacterial Zoonoses Branch, National Center for Infectious Diseases.

We also wish to acknowledge the Minnesota Department of Health for kindly permitting us to borrow liberally from the format and content of their 1995 publication titled "Lyme disease: Guidelines for Minnesota clinicians - epidemiology, microbiology, diagnosis, treatment, and prevention"

Printing and dissemination of this document was supported by Cooperative Agreement U50/CCU514667-01 from the Centers for Disease Control and Prevention.